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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

ART UNIT	PAPER NUMBER
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DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No. 08/950542 Applicant(s) BACHOVCHIN
Examiner D. LUKTON Group Art Unit 1654

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 4/6/99

☒ This action is FINAL.

☒ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 35-51 is/are pending in the application.

Of the above claim(s) is/are withdrawn from consideration.

☐ Claim(s) is/are allowed.

☒ Claim(s) 35-51 is/are rejected.

Claim(s) is/are objected to.

Claim(s) are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The proposed drawing correction, filed on is approved disapproved.

The drawing(s) filed on is/are objected to by the Examiner.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been received.

received in Application No. (Series Code/Serial Number)

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received:

Priority

Priority

Notice of Reference(s) Cited, PTO-892

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-949

Other

Office Action Summary

Pursuant to the directives of paper No. 30 (filed 4/6/99), claims 35-51 have been amended. Claims 35-51 are pending.

Applicants' arguments filed 4/6/99 have been considered and found not persuasive. The prior art rejections are maintained.

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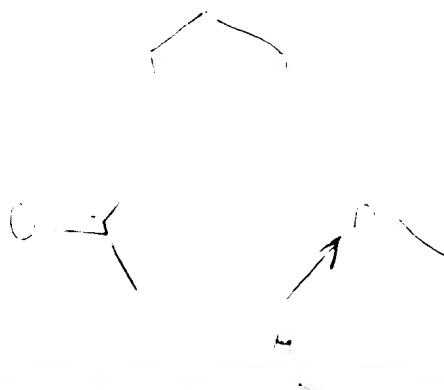
Claim 48 is rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

There is a typographical error in the structure of claim 48. The oxygen atom (of the carbonyl group) should be moved to the left by a distance of about 3 millimeters.

*

Claims 35-51 are rejected under 35 U.S.C. §103 as being unpatentable over Bachovchin (*J. Biol. Chem.* **265**, 3738, 1990).

The teachings of the reference were indicated previously. In response, Bachovchin has argued that his teachings in this article (*J. Biol. Chem.*) were not correct. Specifically, applicant has argued that the following structure is formed:



However, in paragraph 7 of the declaration, there is a contradiction. On the one hand, applicant refers to a "conformation equilibrium on ... a slow time scale". But on the other hand, the last sentence of paragraph 7 states that there is actually a covalent bond that is formed. Either there is a covalent bond or there is not. If there is in fact a covalent bond between the alanyl nitrogen, and the boron that is bonded to the pyrrolidine ring, then perhaps it would appear at first blush that the prior results (*J. Biol. Chem.*, 1990) could be explained by a co-elution (on silica gel) of the L,D-cis and the L,L-cis isomers with one another, and separately, a co-elution of the L,D-trans and L,L-trans isomers. There are, however, three arguments against such a conclusion: (a) applicants have stated in paragraph 7, declaration, that there is a conformational equilibrium, rather than an outright covalent bond formation; (b) even if there were covalent bond formation between nitrogen and boron, the *trans*- isomer would not be "trapped" by the boron atom, i.e., at best, there would be a mixture of covalently bonded "cis" isomers, and structures in which there is no bonding between nitrogen and boron; in the compounds for which no covalent bonding was present, there would be no cis/trans isomerization. (c) applicants have provided an NMR spectrum which is asserted to be that of a "bone-fide" L,L-isomer. However, in describing the compound for which this

the *cis* isomer, or the *trans* isomer, and is there a covalent bond between the nitrogen of the alanine, and the boron of the pyrrolidine ring? While it is plausible that there could be some sort of coordination between the nitrogen of the alanine and the boron of the pyrrolidine ring, applicants arguments in the declaration are otherwise unconvincing. Particularly unlikely is the possibility of a "trans" isomer, given that only a six-membered ring (adjacent to a 5-membered ring) is being proposed. But even if the various contradictions and omissions could be explained, there would still be one remaining fact, which is that the presumption of enablement is conferred upon the *J. Biol. Chem.* paper. If a hypothetical applicant had conducted a series of experiments, and interpreted all of them incorrectly, or if a hypothetical applicant has conducted no experiments at all, but merely renders a groundless assertion, that disclosure is considered to be "enabling", from a legal perspective, once the patent issues. If the presumption of enablement is granted to someone who has never attempted a single experiment, then surely the presumption of enablement should be bestowed upon an article in a respected journal such as the one at issue. If it is really true that the compound isolated in the *J. Biol. Chem.* paper was an N->B covalently bonded *trans*-ring structure, that fact is of little import from a legal perspective. Bachovchin, in the *J. Biol. Chem.* paper characterized the compound, whatever it was, as the L,L-isomer.

pass through silica would provide even higher purity.

Turning next to the arguments of applicants' attorney, she has relied heavily on the argument that it would not have been obvious to switch from silica gel to a C18 matrix. Such an assertion is not challenged, but the extent to which it might be true is of little consequence with regard to the question of novelty. The claims are drawn to compounds (mixtures), not to a method of separation. The path by which the compounds may have been purified is not controlling. The reference has described the means to obtain Ala-boroPro in 95% enantiomeric excess; if the compound has in fact been misidentified, that is of little consequence from a legal standpoint.

Applicants have also made reference to *Biochemistry* **32**, 8723, 1993. If applicants wish to rely on this disclosure, applicants are requested to point out the exact location in the text where it is stated that there is a N->B covalently bonded *trans*-ring structure. Comments by the examiner with regard to this reference will be deferred pending identification of the relevant passage.

Applicants' remaining arguments are found not persuasive; the rejection is maintained.

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Claims 35-51 are rejected under 35 U.S.C. §103 as being unpatentable over Bachovchin (USP 4,935,493) or Bachovchin (WO 89/03223) or Flentke (*Proc Natl*

scope of the claims. Applicants have argued that the reference does not teach a mixture "enriched in the L-isomer", and does not teach a method of separating diastereomers. The examiner does not argue that a mixture of exactly 96 parts L-isomer to 4 parts D-isomer would have been obvious. But the claims do not require this. The claims would encompass, for example a stoichiometry of 10,000,000:1 of the L-isomer to the D-isomer. Thus, for most intents and purposes, the claims don't really require a mixture. The fact is that the organic chemist of ordinary skill would recognize that there are only two possibilities; "D", and "L". When one tosses a coin 20 times, it would be impossible to predict, 20 times in a row, whether "heads" or "tails" would be obtained in each case. However, it can hardly be said that a coin coming up "heads" is a novel or unobvious result. Similarly, given the compound Pro-boroPro, neither the D- nor the L-isomer is unobvious. This is true, even if the separation of isomers has not been attempted. Thus, since the claims require that there be a trace impurity of the D-isomer, the only question is whether the organic chemist of ordinary skill would recognize that chromatographic separations are not always 100% perfect. Clearly, one would recognize that a trace amount of the D-isomer is likely, especially after only 1 pass through a column.

The rejection is maintained.

Serial No. 950,542
Art Unit 1654

- 7 -

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

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Applicants may submit a claim such as the following:

52. *A method of obtaining a mixture consisting of two or more stereoisomers of formula I:*

[formula as recited] *I*

said method comprising the step of eluting a mixture of stereoisomers according to formula I through a C18 chromatographic matrix, whereby in the resulting mixture at least 96% of the carbon atoms bearing boron are of the L-configuration.

No commitment is made by the examiner to allowing such a claim. However, if agreement can be reached as to what constitutes allowable subject matter, such a claim would be considered.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is (703) 308-3213.

An inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

C. Lukton